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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SCHWADRON, RONALD B

ART UNIT	PAPER NUMBER
1644	

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24

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/424,080	ZAVIALOV ET AL.	
	Examiner	Art Unit	
	Ron Schwadron, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 12-19* is/are pending in the application.

4a) Of the above claim(s) *12-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Claims 1,3-5,19 are under consideration. Claims 6-11 have been cancelled. Claim 19 has been added. Claims 1,4,5 have been amended.

RESPONSE TO APPLICANTS ARGUMENTS

2. Regarding applicants comments about the Zav'Yalov et al. and Zarogoylidis et al. references, said references have been considered as per the IDS filed 2/28/2000. FR 2706772 is now of record on the enclosed PTO-892. ***However, the actual contents of said French language patent have not been considered (eg. all that has been considered is that it was cited as an A reference in the search report filed with the instant application).***

3. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1,3-5,19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons elaborated in the previous Office action. Applicants arguments have been considered and deemed not persuasive.

Regarding claim 1, the phrase "corresponding to" in lines 3 and 6 renders the claim indefinite because it is unclear what corresponding means. Claim 19 also recites said term.

Regarding applicants comments, claim 1 still recites "corresponding to" in lines 3 and 6. Said term is also found in new claim 19.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 1 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons elaborated in the previous Office action. Applicants arguments have been considered and deemed not persuasive.

Applicant is in possession of compositions comprising immunosuppressants and bioactive peptides consisting of SEQ ID NO: 1 (also known as alpha-peptoferon), which consists of positions 130-137 of human IFN-alpha, and SEQ ID NO: 2 which consists of variants of SEQ ID NO: 1. Applicant does not disclose any bioactive peptide corresponding to a high affinity binding site/antiproliferative activity other than SEQ ID NOS: 1-2, or any recombinant protein. Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. A description of a genus of peptide or polypeptide sequences may be achieved by means of a recitation of a representative number of peptide or polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Regarding applicants comments, adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. In the instant application, the amino acid itself or isolated protein is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen*

Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016. Applicant has indicated that other examples of the claimed peptides can be produced based on teachings of the specification. However, adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. In the instant application, the amino acid itself or isolated protein is required.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claim 1 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Charak et al. (Cancer Research 1992 Dec; 52: 6482-6486) in view of Cruse et al. (Illustrated Dictionary of Immunology. CRC Press, New York, 1995; pages 168-169) for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Charak et al. teach a composition comprising immunosuppressants, for example, cyclosporin A, and interferon following chemotherapy to generate an anti-tumor effect and that adoptive transfer of MHC-bearing cells to secondary tumor bearers treated with chemotherapy showed potent antitumor effect (see the abstract, Tables I and 4 in particular). Treatment with IFN and cyclosporin A was started on day 8 and continued up to day 21 and as the combination therapy was given to mice, it be considered a pharmaceutical composition (see page 6483, left column, lines 4-6 in particular). Charak et al. further teach that many patient with tumors other than melanoma are not

suitable candidates for ratiotherapy, and treatment modalities not involving the use of irradation need to be developed. Charak et al. teach that the rationale for combining cyclosporin A and IFN in augmenting the antitumor effect was "based on the data suggesting that the cytolytic action of CSA-generated cells was related to the expression of class II MHC antigens and that IFN enhances the expression of class II antigens on the tumor cells (i.e. MHC-unrestricted cytotoxic potential; see the Abstract and page 6482, right column, paragraph 2 in particular). Charak et al. do not teach a recombinant protein carrying the sequences corresponding to the structures of IFN alpha, beta, omega, or tao. Cruse et al. teach interferons which are a group of regulatory proteins which have immunomodulatory functions. Interferons alpha and beta are type I interferons, and interferon alpha is anti-proliferative (see bottom of page 168, right column, page 169, left column and top of right column in particular). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted the specific IFNs taught by Cruse et al. in the composition comprising immunosuppressants and generic interferon taught by Charak et al. because they have the same immunomodulatory activity. One of ordinary skill in the art would have been motivated to do this because the interferons are immunomodulatory and anti-proliferative and exhibit the same functional characteristics. Further, Charak et al. teach that combining cyclosporin A and IFN augments the antitumor effect. Although neither reference specifically teaches a recombinant protein, a protein is a protein irrespective of how it is made, and would function in the same manner.

Regarding applicants comments, none of the claims under consideration are drawn to methods. The instant claims are drawn to compositions. The recitation of an intended use carries no patentable weight in the instant composition claims. The instant rejection renders obvious the claimed invention for the reasons enunciated above. Regarding the particular quotes from the specification to which applicant refers, Charak et al. teach use of cyclosporin and inteferon to treat melanoma in an art recognized mouse model. Furthermore, cyclosporin is an art known agent that is routinely used in clinical transplantation.

9. Claims 1, 3, 5, 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Charak et al. (Cancer Research 1992 Dec; 52: 6482-6486) in view of Zav'Yalov et al. (Molecular Immunology 1995; 32(6): 425-431; IDS document) for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Charak et al. has been discussed supra. Charak et al. do not teach SEQ ID NOS: 1 (also known as alpha-peptoferon) or 2. Zav'Yalov et al. teach a bioactive peptide comprising positions 130-137 (i.e. an 8-mer) of interferon-alpha2 (authors definition: alpha-peptoferon) which is a bioactive peptide and displaces labeled IFN-alpha2 from the IFN-alpha2/receptor complex, meaning that it interacts with the high-affinity binding site of IFN-alpha2 (see the abstract and page 425, left column, and page 427, right column in particular). The mouse and human IFN-alpha2 shown in Figure 1 comprises SEQ ID NO: 1 with a single substitution at position 131 from "T" to "R" or "K", respectively which meets the claim limitation of a variant of SEQ ID NO:1 that is SEQ ID NO: 2, such that one amino acid of SEQ ID NO: 1 is substituted. Zav'Yalov et al. further teach that the amino acid sequences of IFN-alphas and IFN-beta from positions 123-140 are most highly conserved, therefore, a bioactive peptide comprising positions 130-137 of interferon-beta would have the same functional activity as interferon-alpha2. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted the SEQ ID NOS 1-2 taught by Zav'Yalov et al. in the composition comprising immunosuppressants and generic interferon taught by Charak et al. because they both contain the high affinity binding site/anti-proliferative activity. One of ordinary skill in the art would have been motivated to do this because the composition comprising the immunosuppressants and interferon protein or peptides corresponding to the high affinity binding site/anti-proliferative activity augments the antitumor effect.

Applicants arguments have been addressed in paragraph 8 of this Office Action.

10. Claim 4 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Charak et al. (Cancer Research 1992 Dec; 52: 6482-6486) in view of Zav'Yalov et al. (Molecular Immunology 1995; 32(6): 425-431; IDS document) as applied to claims 1, 3,

5, 19 above, and further in view of Isoai et al. (Cancer Research 1994 March; 54: 1264-1270) for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

The Charak et al. and Zav'Yalov et al. references have been discussed supra. The combined reference teachings do not teach one of the peptides bound to a small molecular or macromolecular substance to increase the stability of the peptide. Isoai et al. teach a peptide chemically coupled to albumin to form stable entities – and the conjugate was more stable than the peptide alone (see the abstract in particular). Further, albumin was chosen because it is the most abundant and stable protein in serum and would increase the half-life of the peptide (see page 1264, right column, paragraph 3 in particular). The peptide albumin conjugate was used to target tumor cells wherein the peptide would bind its receptor (see the abstract in particular).
It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted the albumin-peptide conjugate taught by Isoai in the bioactive peptide taught by Zav'Yalov et al., and further substitute the IFN-alpha-albumin conjugate in the composition comprising cyclosporin and interferon taught by Charak et al. to increase the stability of the IFN peptides in the pharmaceutical composition and exhibit antitumor effect. One of ordinary skill in the art would have been motivated to do this because the stability of the peptide was so much greater when conjugated to albumin as taught by Isoai et al. to target tumor cells, and the composition comprising cyclosporin and IFN-alpha bioactive protein of peptide augments the antitumor effect.

Applicants arguments have been addressed in paragraph 8 of this Office Action.

11. Claims 1, 3, 5,19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Charak et al. (Cancer Research 1992 Dec; 52: 6482-6486) in view of WO 94/01457 or Ruegg et al. (Journal of Interferon Research 1990; 10: 621-626) for the reasons elaborated in the previous Office action. Applicants arguments have been considered and deemed not persuasive.

The Charak et al. reference has been discussed supra. Charak et al. do not teach SEQ ID NO: 1 (claims 3, 5, and 8-10). The WO 94/01457 document teaches a polypeptide comprising SEQ ID NO: 1 of the instant application which is an interferon-receptor binding peptide (i.e. bioactive peptide; see claim 4 and SEQ ID NO: 4 of the

WO document in particular) which are designed for pharmaceutical compositions (see page 2, paragraph 3 in particular). The multitude of "specific peptides are capable of recognizing and binding to cell surface receptors" which include amino acids 123-140 of Type I Interferons (e.g. alpha and beta); wherein the critical epitopes for Type I IFN receptor recognition are associated with the residues 130-140 for all species of Type I IFNs (see page 7, paragraph 1; page 8, paragraph 2; and page 19, paragraph starting at line 1 in particular). Furthermore, the WO 94/01457 document teaches that IFNs affect cellular functions, such as cell growth control, and the "ability of IFNs to modulate cell growth is observed with many cell types and is particularly effective in the case of tumor cells (see page 1, paragraph 3 in particular). Ruegg et al. teach a decapeptide of human interferon-alpha (i.e. a bioactive peptide) which inhibits the proliferation of lymphoblastoid cell lines with a half-maximal inhibitory concentration (see the abstract, and page 622, paragraph 2 in particular). Further, "the peptide inhibited T-cell proliferation in a sequence-specific and dose-dependent manner similar to that seen for intact IFN-alpha" (see Figures 2A and 2B in particular). Although the peptides does not include the regions of IFN-alpha that are required for receptor binding, it does have anti-lymphoproliferative activity (see page 623, lines 3-4 in particular). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted the bioactive IFN-alpha/beta bioactive peptides taught by WO 94/01457 or Reugg et al. in the composition comprising cyclosporin and interferon taught by Charak et al. because they share the same high affinity binding site/antiproliferative site and would therefore, exhibit the same anti-proliferative effect. One of ordinary skill in the art would have been motivated to do this because the structure and function of the peptides taught by WO 94/01457 and Reugg et al. share the same immunomodulatory action as the composition comprising cyclosporin and generic interferon protein taught by Charak et al. and would augment the antitumor effect.

Applicants arguments are addressed in paragraph 8 of the instant Office action.

12. Claim 4 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Charak et al. (Cancer Research 1992 Dec; 52: 6482-6486) in view of WO 94/01457 or Ruegg et al. (Journal of Interferon Research 1990; 10: 621-626) as applied to claims 1,

3, 5, 19 above, and further in view of Isoai et al. (Cancer Research 1994 March; 54: 1264-1270).

The Charak et al., WO 94/01457 and Reugg et al. references have been discussed supra. The combined reference teachings do not teach coupling the peptide to a small molecular or macromolecular substance to increase the stability of the peptide in a composition. Isoai et al. teach a peptide chemically coupled to albumin to form stable entities – and the conjugate was more stable than the peptide alone (see the abstract in particular). Further, albumin was chosen because it is the most abundant and stable protein in serum and would increase the half-life of the peptide (see page 1264, right column, paragraph 3 in particular). The peptide albumin conjugate was used to target tumor cells wherein the peptide would bind its receptor (see the abstract in particular). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted the albumin-peptide conjugate taught by Isoai in the interferon peptides taught by WO 94/01457, or Ruegg et al., and further substitute the interferon alpha/beta—albumin conjugates in the composition of cyclosporin and interferon taught by Charak et al., to increase the stability of the peptides in the pharmaceutical composition to increase the half-life of the composition. One of ordinary skill in the art would have been motivated to do this because the stability of the peptide was so much greater when conjugated to albumin as taught by Isoai et al. to target tumor cells, and the composition comprising cyclosporin and interferon taught by Charak et al. augments the antitumor effect.

Applicants arguments are addressed in paragraph 8 of this Office Action.

13. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Charak et al. (Cancer Research 1992 Dec; 52: 6482-6486) in view of WO 94/10313 (IDS document).

The Charak et al. reference has been discussed supra. The Charak et al. reference does not teach compositions comprising IFN-tau bioactive peptides. The WO 94/10313 document teaches interferon-tau (IFN-tau) peptides (i.e. bioactive peptide) having anti-cellular proliferation properties that do not have the cytotoxic side-effects when used to treat cells (see page 34, line 31 in particular). Further, the WO document teaches that the usefulness of IFN-alpha's has been limited by their toxicity in the treatment of cancer that leads to side-effects (see page 7, lines 11-15 in particular). The IFN-tau polypeptides and peptides were used to target human carcinoma and mammary tumor

cells (i.e. cancer) for growth inhibition (i.e. anti-lymphoproliferative; see page 7, lines 30-35 in particular). Anti-proliferative IFN-tau peptides were identified comprising amino acids 119-150 which would be useful alone or recombinantly or covalently fused to other proteins (such as serum albumin) which would increase stability (see page 30, lines 27-35; page 31, lines 1-4; page 34, lines 26-32; and page 35, lines 10-14 and 23-35 in particular). Antibodies which bound the peptide 119-150 prevented binding of IFN-tau to its receptor (i.e. the peptide 119-150 comprised the receptor binding site; see page 31, lines 5-9 in particular). The WO document encompasses IFN-tau peptides to "inhibit, prevent, or slow tumor growth" and pharmaceutically useful compositions (see page 40, lines 32-33; page 41, lines 15-17 and 34-35 in particular). Example 15C describes the anti-proliferative activity of the IFN-tau peptides wherein peptide 119-150 was the most effective inhibitor of anti-proliferative activity (see pages 78-79 in particular). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted the IFN-tau bioactive peptides taught by WO 94/10313 in the composition comprising cyclosporin and generic interferon taught by Charak et al. to augment antitumor activity. One of ordinary skill in the art would have been motivated to do this because both the IFN-tau peptide taught by WO 94/10313 and the IFN taught by Charak exhibit anti-proliferative activity when combined in a composition would anti-tumor activity.

Applicants arguments are addressed in paragraph 8 of this Office Action.

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 1600 at (703) 308-4242.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

Ron Schwadron, Ph.D.
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Art Unit 1644